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Maternal cardiac adaptation and fetal growth

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Condensation: Maternal cardiac adaptation from 32 weeks' gestation parallels fetal growth and oxygenation; babies with birthweight <20th percentile demonstrate worsening fetal cerebroplacental ratio and maternal hemodynamics.

Short title: Maternal cardiac function and fetal growth.

AJOG at a glance:

A. We aimed to investigate longitudinally the trends in maternal cardiac function, fetal growth and oxygenation, with advancing gestation.
B. There were similar trends in fetal growth and maternal cardiac function with advancing gestational age. From 32 weeks' gestation, fetuses with lower estimated fetal weight continued with a decelerative growth pattern and reduced cerebroplacental ratio whilst fetuses with greater estimated fetal weight had an accelerative growth pattern with increased cerebroplacental ratio. The deviation in fetal growth pattern occurred at the same time when women with smaller fetuses experienced a decline in cardiac output and increase in peripheral vascular resistance, whilst women with bigger fetuses continued to adapt favourably with greater cardiac output and lower peripheral vascular resistance.
C. Maternal cardiac adaptation from 32 weeks' gestation parallels fetal growth and oxygenation.

ABSTRACT

Background: Pregnancies with small for gestational age fetuses are at increased risk of adverse maternal-fetal outcomes. Previous studies examining the relationship between maternal hemodynamics and fetal growth were mainly focused on high risk pregnancies and those with fetuses with extreme birthweights such as less than the 3rd or 10th percentile and assumed a similar growth pattern in fetuses above the 10th percentile throughout gestation.

Objective: To evaluate the trends in maternal cardiac function, fetal growth and oxygenation with advancing gestational age in a routine obstetric population and all ranges of birthweight percentiles.

Study design: This was a prospective, longitudinal study assessing maternal cardiac output and peripheral vascular resistance by bioreactance at 11^{+0}-13^{+6}, 19^{+0}-24^{+0}, 30^{+0}-34^{+0} and 35^{+0}-37^{+0} weeks' gestation, sonographic estimated fetal weight in the last three visits and the ratio of the middle cerebral artery by the umbilical artery pulsatility indices or cerebroplacental ratio in the last two visits. Women were divided into five groups according to birthweight percentile: Group 1 <10th percentile (n=261); group 2, 10-19.9 percentile (n=180), group 3, 20-29.9 percentile (n=189); group 4, 30-69.9 percentile (n=651) and group 5, ≥70th centile (n=508). Multilevel linear mixed-effects model was performed to compare the repeated measures of hemodynamic variables and z-scores of estimated fetal weight and cerebroplacental ratio.

Results: In visit 2, compared to visit 1, in all groups cardiac output increased and peripheral vascular resistance decreased. At visit 3, groups 1, 2 and 3, compared to 4 and 5, demonstrated an abrupt decrease in cardiac output and increase in peripheral vascular resistance. From visit 2, group 1 had a constant decline in estimated fetal weight, coinciding with the steepest decline in maternal cardiac output and rise in peripheral vascular resistance. In contrast, in groups 4 and 5 the estimated fetal weight had a stable or accelerative pattern, coinciding with the greatest increase in cardiac output and lowest peripheral vascular resistance. Groups 2 and 3 showed a stable

growth pattern with intermediate cardiac output and peripheral vascular resistance. Increasing birthweight was associated with higher cerebroplacental ratio. Groups 3,4 and 5 had stable cerebroplacental ratio across visits 3 and 4, whilst groups 1 and 2 demonstrated a significant decline.

Conclusion: in a general obstetric population, maternal cardiac adaptation from 32 weeks' gestation parallels the pattern of fetal growth and oxygenation; babies with birthweight <20th percentile have progressive decline in fetal cerebroplacental ratio, decline in maternal cardiac output and increase in peripheral vascular resistance.

KEYWORDS: pregnancy, hemodynamics, cardiac output; peripheral vascular resistance, small for gestational age, fetal growth pattern, cerebroplacental ratio, bioreactance, biometric parameters

INTRODUCTION

Newborn size is related to maternal anthropometric factors, such as height, pre-pregnancy weight status and gestational weight gain,[1] and the intrauterine environment immediately prior to delivery, which could be affected by the degree of successful placentation and maternal health throughout pregnancy. Traditionally, fetuses with birthweight <10th percentile are classified as small for gestational age (SGA) and they are at higher risk of adverse outcomes.[2-6] However, adverse outcomes are not confined to this group. Indeed, there is evidence that there is a proportionate rise in perinatal mortality, adverse neonatal outcomes and intrapartum compromise as the birthweight falls <50th centile.[7-9] Even fetuses with birthweight between 50th and 75th percentile still represent an 'at risk' group.[7] Although there is no consensus on the optimal birthweight percentile, the perinatal and intrapartum risks appear to plateau when the birthweight is >75th percentile.

Women who deliver SGA babies have suppressed cardiac output (CO) and raised peripheral vascular resistance (PVR)[10-14]. Previous studies demonstrate the existence of a relationship between fetal size and fetoplacental Doppler findings with maternal cardiovascular response to pregnancy.[15,16] However, they were mainly cross-sectional, focused on high risk populations and the extremes of birthweight, assuming a similar fetal growth pattern in non-SGA groups.. Cerebroplacental ratio (CPR), a marker of fetal oxygenation, is commonly used to differentiate fetal growth restriction (FGR) from SGA.[17] In the third trimester, CPR has been associated with intrapartum fetal compromise, increased rate of cesarean delivery and admission to the neonatal unit. [18-21] We have previously demonstrated that in cases of SGA fetuses, maternal hemodynamics deviate most markedly in those with reduced CPR.[22]

The objective of this study was to investigate longitudinally, in a routine obstetric population stratified according to birthweight percentile, the trends in maternal cardiac function, fetal growth and oxygenation, assessed by the CPR, with advancing gestational age.

MATERIALS AND METHODS

Study population

Women with singleton pregnancies attending routine pregnancy care at 11^{+0} to 13^{+6} weeks' gestation in six maternity hospitals in the UK between November 2015 and May 2016 were invited to participate in the study for longitudinal maternal hemodynamic and fetal assessment and 1,918 (99% of those approached) agreed. Gestational age was confirmed from the measurement of fetal crown-rump length.[23] After the first visit, 13 pregnancies were diagnosed with fetal anomalies, and 16 resulted in subsequent miscarriage or termination due to fetal abnormalities. After exclusion of those with poor signals, missing pregnancy outcomes and those who withdrew consent from the study, a total of 1,789 women were followed up at 19^{+0} to 24^{+0}, 30^{+0} to 34^{+0} and 35^{+0} to 37^{+0} weeks' gestation (Figure 1). During each of these visits we measured maternal weight and blood pressure and assessed cardiovascular function non-invasively. In visits 2, 3 and 4, we recorded the ultrasonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) and calculated the estimated fetal weight (EFW).[24] In addition, in visits 3 and 4, we performed fetal Doppler studies for measurement of umbilical artery pulsility index (UA-PI) and middle cerebral artery pulsility index (MCA-PI). The study was approved by the NHS Research Ethics Committee (REC reference: 13/LO/1479).

Maternal factors and pregnancy outcomes

Maternal factors recorded included age, height, weight and body surface area (BSA), racial origin (White, Black, South Asian, East Asian and mixed), methods of conception (spontaneous or artificial reproductive techniques (ART)), cigarette smoking, chronic hypertension, diabetes mellitus and parity (nulliparous, parous with and without previous preeclampsia). Pregnancy outcomes included preeclampsia (PE), pregnancy induced hypertension (PIH), gestational diabetes mellitus (GDM), gestational age at delivery,

preterm birth, induction of labour, operative delivery for fetal distress, birthweight and perinatal mortality.

Maternal cardiovascular function and fetal biometry and Dopplers

Maternal cardiac function was assessed using a non-invasive, bioreactance technology (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) which we have previously validated for use in pregnancy.[25] The bioreactance technology uses the simultaneous relative phase shifts to calculate SV when an alternating electrical current traverse the thoracic cavity. After 15 minutes of rest, four electrodes were applied across the maternal back and cardiac variables [CO, SV, HR, PVR and mean arterial pressure (MAP)] were recorded in a sitting position for 10 minutes at 30-second intervals (20 cycles). The averages of the final 10 cycles of hemodynamic variables were included in the analysis.

EFW and fetal biometry HC, AC and FL z-scores were calculated based on the formulae derived from normal ranges in 1040 singleton pregnancies.[26] The CPR was calculated as the ratio between the MCA-PI and UA-PI, measured as described by Vyas et al.[27]

Definitions

Birthweight percentile for gestational age was derived from the Fetal Medicine Foundation reference range.[28] We classified the study population into five groups based on birthweight percentiles: group 1, <10th percentile; group 2, 10th-19.9th percentile, group 3, 20th-29.9th percentile; group 4, 30th-69.9th percentile and group 5, ≥70th centile. The definitions of PE and PIH were those of the International Society for the Study of Hypertension in Pregnancy.[29]

Statistical analysis

We examined the longitudinal changes of maternal cardiovascular variables and z-scores of fetal biometry, EFW and CPR stratified according to the birth weight percentile groups as described above. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of numerical data. For comparison of continuous data, the Kruskal-Wallis or the one-way ANOVA tests were used for not-normally and normally distributed data,

respectively. For categorical data the chi-square test or Fisher's exact test were used, where appropriate. Data are presented as median (interquartile range) and mean (standard deviation) for not-normally and normally distributed continuous variables, respectively, and as n (%) for categorical variables. The distribution of maternal weight, CO, SV, MAP and PVR were made Gaussian after $\log_{10}$ transformation.

We performed a multilevel linear mixed-effects model for the repeated measures analysis of the maternal hemodynamic variables and ultrasound assessment of fetal biometry z-scores (EFW, HC, AC, FL) and CPR controlling for maternal age, maternal body surface area (BSA), racial origin, smoking, previous PE or FGR, parity, maternal chronic hypertension and diabetes, pregnancy related complications such as PE, PIH and GDM, birthweight percentile group, time (the four visits) and the interaction between birthweight group and time. The likelihood radio (LR) test was used to define the best multilevel model comparing the base model to either the random intercept or random intercept and slope. The estimated marginal means of each hemodynamic variable, fetal biometry and CPR at each birthweight percentile group/time combination are presented.

The software program IBM SPSS was used for the statistical analysis (SPSS Statistics for Windows 2015 Version 25.0, Armonk, NY: IBM Corp).

RESULTS

In total, 1,789 women were included in the final analysis of the longitudinal changes in maternal hemodynamics and fetal biometry z-scores. The five groups included 261 women in group 1, 180 in group 2, 189 in group 3, 651 in group 4 and 508 in group 5.

Maternal demographics and pregnancy outcomes

The maternal demographic characteristics and pregnancy outcomes are presented in Table 1. There was no significant difference in maternal age or prevalence of ART among the five birthweight groups. However, there was a significant difference in the BSA, smoking, racial origin, parity, previous PE or FGR and chronic hypertension,

gestational age of delivery, proportion of women who underwent induction of labour, operative birth for fetal distress, and perinatal mortality between the five birthweight groups. There was no difference in the prevalence of PE, PIH, GDM, rates of emergency cesarean section and neonatal unit admission.

Maternal hemodynamic changes in different birth weight groups

The fixed effects of the best multilevel models and the pairwise comparison of estimated marginal means with 95% confidence intervals (CI) are shown in Tables 2-4 and Figure 2 for $Log_{10}CO$, $Log_{10}PVR$, EFW and CPR. For maternal HR, $Log_{10}SV$ and $Log_{10}MAP$ and fetal HC, AC, and FL Z-scores results are shown in Supplementary results, Supplementary Tables 1-2 and Supplementary Figures 1-2.

For all maternal hemodynamic and fetal biometry and Doppler variables (apart from HR and $Log_{10}PVR$), a random intercept–random slope model provided a significantly better fit to the data than did the base model or a random intercept model (data not presented).

$Log_{10}CO$, $Log_{10}PVR$, EFW and CPR: relationship with maternal demographic characteristics (Table 2)

Increasing maternal age was associated with a decrease in $Log_{10}CO$ and higher $Log_{10}PVR$. Increasing BSA was associated with higher $Log_{10}CO$ and lower $Log_{10}PVR$. Compared to women of White racial origin, women of Black, South Asian, and East Asian origin had lower $Log_{10}CO$ and women of South Asian and East Asian had higher $Log_{10}PVR$. Compared to nulliparous women, parous women with no previous PE and/or SGA had significantly higher $Log_{10}CO$ and lower $Log_{10}PVR$. Women in groups 1-3 had lower $Log_{10}CO$ and groups 1 and 2 higher $Log_{10}PVR$ compared to those in group 5. Women with hypertensive disorders, compared to non-affected women, had significantly lower $Log_{10}CO$ with higher $Log_{10}PVR$. Similarly, women with chronic hypertension have higher $Log_{10}PVR$ but there was no significant difference in $Log_{10}CO$. Women with GDM

demonstrated lower $Log_{10}CO$ and higher $Log_{10}PVR$. There was significant interaction between birthweight groups and time for $Log_{10}CO$ and $Log_{10}PVR$.

Women with greater BSA had greater EFW. Compared to nulliparous, parous women with no previous PE and/or SGA had lower EFW. Compared to group 5, fetuses in all other groups had significantly smaller EFW. PE was associated with lower EFW, chronic hypertension was associated with lower EFW whilst PIH had no significant contribution to fetal measurements. Gestational diabetes had no significant contribution to all fetal measurements.

Compared to fetuses of White women, Black women had fetuses with higher CPR. Groups 1 to 4, compared to those in group 5, had significantly lower CPR. Women with chronic hypertension had fetuses with lower CPR. There was significant interaction between birthweight groups and time for all the fetal biometry and CPR measurements.

$Log_{10}CO$, $Log_{10}PVR$, EFW and CPR: changes with time after controlling for maternal characteristics and outcomes (Tables 3 and 4, Figure 2)

In the first two visits, there was no difference between groups and all of them demonstrated a similar increase in $Log_{10}CO$ and a decline in $Log_{10}PVR$. At the third visit, a divergence in maternal hemodynamics between groups was observed for the first time and this peaked at the fourth visit. For example, the mean difference in CO between groups 1 and 5 increased from 1.062 (95% CI: 1.058, 1.065) at visit 3 to 1.084 (95% CI: 1.080, 1.087) at visit 4.

Although all groups demonstrated a decline in $Log_{10}CO$, this was more abrupt in groups 1 and 2-3, compared to 4 and 5. For example, group 1 had the most significant decline in CO, with a difference of 1.074 (95% CI:1.069, 1.079). This decline was the greatest and occurred earlier compared to groups 2 to 5 which demonstrated a smaller and later decline in CO from visit 3 onwards (group 2=1.049 (95% CI: 1.045, 1.054),

group 3=1.039 (95% CI: 1.035, 1.045), group 4=1.032 (95% CI: 1.030, 1.035) and group 5=1.028 (95% CI: 1.025, 1.030).

Log_{10}PVR, continued its decline in all groups in visit 3, apart from group 1, which demonstrated an increase from visit 2. At the fourth visit, all groups continued declining their Log_{10}CO and increased Log_{10}PVR with the worst values for groups 1 and 2 and best for 4 and 5.

In group 1, the EFW was the lowest and in group 5 the highest throughout all visits. Group 4 demonstrated similar trends to group 5 but all biometry values were closer around the zero Z-score, which is equivalent to the 50th percentile. Groups 2 and 3 demonstrated similar trends with values remaining below the 50th percentile.

Groups 1 and 2 demonstrated significantly worsening CPR when compared to Group 5 with increasing CPR. For example, at visit 3, Group 1 has a CPR that was -0.427 (95% CI: -0.444, -0.409) z-scores lower than Group 5. This difference increased to -0.726 (95% CI: -0.278, -0.244) at visit 4.

COMMENT

Principle findings

The results of this study demonstrate that there is a similar trend in fetal growth and maternal cardiac function with advancing gestational age from 32 weeks of gestation onwards. Fetuses destined to be smaller had lower EFW from 20 weeks' gestation and continued with a static or decelerative growth pattern; these fetuses had reduced CPR from 32 weeks' gestation onwards. On the contrary, fetuses destined to be bigger had greater EFW from 20 weeks' gestation and demonstrated an accelerative growth pattern; these fetuses had increased CPR from 32 weeks' gestation onwards. The deviation in fetal growth pattern occurred at the same time when women with smaller fetuses (groups 1,2 and 3) experienced a sharp decline in CO and increase in PVR, whilst women with

bigger fetuses (groups 4 and 5) continued to adapt favourably with greater CO and lower PVR.

We chose to adjust the maternal hemodynamic variables to maternal height and weight instead of using indexed values to BSA. Indexing cardiac measurements assumes a proportionate relationship between height and weight and it is unclear if this is the case in pregnancy.[30,31] In addition, there is a risk that by using indexed cardiac measurements, we could be normalising the cardiac variables in women who are transitioning to a disease state in parallel with weight gain. Finally, it is unclear which of the formulae for BSA one should use. The commonest formula had been estimated by examining only nine subjects[32] and none of them have been validated in pregnancy.

Results

This is the first study which explores the relationship between longitudinal changes in maternal hemodynamics with concurrent ultrasonic assessment of fetal growth and Doppler stratified according to different birthweight groups, in a general obstetric population. Previous studies have primarily focused on characterizing maternal hemodynamic profiles in high risk populations and in the extremes of birthweight. These studies were mostly cross-sectional, and compared the hemodynamic profiles in women with FGR and that of normal pregnancies,[10,33,34] or growth restricted and non-growth restricted SGA pregnancies.[12,35] Most studies were conducted in high-risk pregnancies, such as women with chronic hypertension and previous PE or PIH[11] or with known diagnosis of SGA/FGR.[22,36] There was one longitudinal study that assessed 64 women from a general population from pre-conception to the third trimester and suggested that incremental CO from pre-pregnancy to second trimester is related to fetal growth from the second to third trimester.[37] However, maternal characteristics which could affect fetal growth and hemodynamics were not adjusted for. Furthermore, as only the mean birthweight of the population was reported, disparate growth trajectories between SGA or LGA babies and their respective maternal hemodynamics could not be assessed.

Clinical implications

Previous studies that showed distinct maternal hemodynamic changes associated with SGA or FGR, suggested that these were evident as early as pre-conception,[38] first trimester[11,39] at the time of diagnosis[13] and persisted well into late third trimester.[10] However, in our study, after adjusting for maternal size and medical conditions, we demonstrated that between visit 1 and 2, most women adapted favourably to pregnancy by increasing CO and decreasing PVR irrespective of birthweight groups. It is possible that in the general population, maternal cardiac adaptation may not be the main drive for fetal growth in early pregnancy; subsequently when the metabolic needs of the feto-placental unit increase a potential maternal cardiovascular decompensation may disturb the balance between demand and supply of nutrients. In addition, the results of the above-mentioned studies in high-risk populations before 20 weeks could be explained by the use of medications, which may impair either the already compromised maternal cardiovascular system or affect the fetus itself from early pregnancy.

Conventionally, deficient remodelling of the spiral arteries and placental bed ischemia, has been implicated in the etiology of early-onset SGA, which is usually easily identified clinically.[40-42] This is represented in our data by group 1, which represented the most extreme end of smallness and had a constant decline in all variables of fetal biometry and CPR, coinciding with the steepest decrease in maternal CO and rise in PVR from 32 weeks. On the opposite end, groups 4 and 5 had optimal growth, Dopplers and maternal cardiac function and demonstrated the true “low risk pregnancies” in terms of fetal growth. Groups 2 and 3 are clinically the most challenging groups. They have similar fetal growth patterns and in terms of maternal hemodynamics they have CO and PVR in between the worse and best groups. However, group 2 showed a sharp decline in CPR after 32 weeks, whilst group 3 had a stable pattern. Group 2 therefore, represents a vulnerable group for late-onset FGR which can be missed with current guidelines.

Research implications

Further research is needed as to whether it may not be appropriate to consider fetuses between 10th to 20th percentiles to be AGA throughout pregnancy and whether maternal hemodynamics after 20 weeks gestation may help identify pregnancies at risk of late-onset FGR. Maternal hemodynamics could be used as a contingent screening tool to identify fetuses at significant risk of further deterioration in growth closer to term. In the third trimester, a non-operator dependant maternal hemodynamic assessment could be useful, either because serial ultrasound assessments may not be readily available, or because its accuracy is limited by the inherent error of fetal biometry measurements due to advanced gestation.[43]

Strengths and limitations

The strengths of this study include the large sample size and the concurrent longitudinal assessment of maternal cardiac variables and fetal size. Furthermore, factors such as maternal anthropometric and medical conditions which could affect maternal hemodynamics and fetal growth were adjusted for in both maternal cardiac parameters, fetal biometry and CPR. One of the limitations is that, this study was not powered to study perinatal morbidity in different birthweight percentile groups. The other limitation is that we could not assess maternal hemodynamics before 11 weeks' gestation due to the timing of recruitment; therefore, we are not able to comment if there were any differences in cardiac adaptation preceding placental implantation.

CONCLUSION

Maternal cardiac adaptation from 32 weeks' gestation parallels fetal growth and oxygenation. Babies with birthweight<20th percentile have progressive decline in fetal CPR, maternal CO and increase in PVR and they need closer monitoring, especially closer to term.

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473

Variables	Group 1 (n=261)	Group 2 (n=180)	Group 3 (n=189)	Group 4 (n=651)	Group 5 (n=508)	p-value
Age in years	30.7 (± 5.7)	30.7 (± 5.4)	30.8 (± 5.3)	31.3 (± 5.2)	31.6 (± 5.2)	.064
Body surface area	1.7 (1.6 – 1.8)	1.7 (1.6 – 1.8)	1.7 (1.6 – 1.9)	1.7 (1.6 – 1.9)	1.8 (1.7 – 1.9)	.000
Smoking	24 (9.2)	10 (5.6)	12 (6.3)	29 (4.5)	21 (4.1)	.033
Racial origin						.000
White	174 (66.7)	106 (58.9)	129 (68.3)	500 (76.8)	413 (81.3)	
Black	49 (18.8)	40 (22.2)	37 (19.6)	94 (14.4)	57 (11.2)	
South Asian	26 (10.0)	21 (11.7)	13 (6.9)	24 (3.7)	14 (2.8)	
East Asian	6 (2.3)	3 (1.7)	8 (4.2)	14 (2.2)	9 (1.8)	
Mixed	6 (2.3)	10 (5.6)	2 (1.1)	19 (2.9)	15 (3.0)	
Nulliparous	165 (62.8)	104 (57.8)	119 (63.0)	327 (50.2)	219 (43.1)	.000
Multiparous						.000
Previous PE or FGR	33 (12.6)	17 (9.4)	8 (4.2)	36 (5.5)	24 (4.7)	
No previous PE or FGR	64 (24.5)	59 (32.8)	62 (32.8)	288 (44.2)	265 (52.2)	
Artificial reproductive techniques	6 (2.3)	7 (3.9)	7 (3.7)	12 (1.8)	11 (2.2)	.398
Chronic hypertension	9 (3.4)	8 (4.4)	5 (2.6)	10 (1.5)	5 (1.0)	.020
Pre-existing diabetes	2 (0.8)	1 (0.6)	3 (1.6)	4 (0.6)	4 (0.8)	.748
Pregnancy outcomes						
Gestational age at birth in weeks	39.0 (37.7 – 40.1)	39.6 (38.7 – 40.6)	39.7 (38.7 – 40.6)	40.0 (39.0 – 40.9)	40.1 (39.1 – 41.0)	.000
Preeclampsia	14 (5.4)	5 (2.8)	7 (3.7)	14 (2.2)	13 (2.6)	.116
Pregnancy induced hypertension	12 (4.6)	9 (5.0)	2 (1.1)	22 (3.4)	16 (3.4)	.216
Gestational diabetes	14 (5.4)	5 (2.8)	8 (4.2)	26 (4.0)	27 (5.3)	.572
Induction of labor	99 (37.9)	54 (30.0)	58 (30.7)	163 (25.0)	156 (30.7)	.004
Emergency cesarean	54 (20.7)	26 (14.4)	33 (17.5)	96 (14.7)	98 (19.3)	.111
Operative birth (fetal distress)	46 (17.6)	18 (10.0)	23 (12.2)	71 (10.9)	51 (10.0)	.025
Neonatal unit admission	21 (8.0)	11 (6.1)	8 (4.2)	30 (4.6)	30 (5.9)	.285
Perinatal mortality	4 (1.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	.001

Table 1. Demographic characteristics and pregnancy outcomes of the study groups.

Values given as mean (± standard deviation), median (interquartile range) or n (%). PE= pre-eclampsia; FGR = fetal growth restriction.

The five groups were compared using the chi-square test or Fisher's exact test for categorical variables. The Kruskal-Wallis test or the one-way ANOVA tests with post hoc analysis was used for not-normally and normally distributed data, respectively.

Table 2. Fixed effects of multilevel linear mixed-effects models for Log_{10} cardiac output and Log_{10} peripheral vascular resistance, estimated fetal weight and cerebroplacental ratio z-score.

Parameter	Log_{10} Cardiac output	Log_{10} Peripheral Vascular	Estimated fetal weight	Cerebroplacental ratio

			Resistance		z-score		z-score	
Fixed part	Estimate (Standard error)	p-value	Estimate (Standard error)	p-value	Estimate (Standard error)	p-value	Estimate (Standard error)	p-value
Intercept	0.599 (0.022)	<.0001	3.120 (0.024)	<.0001	0.109 (0.231)	<.001	0.190 (0.046)	.010
Age (years)	-0.002 (0.000)	<.0001	0.002 (0.0004)	<.0001				
Body surface area	0.141 (0.009)	<.0001	-0.076 (0.010)	<.0001	0.564 (0.114)	<.001		
Race (reference White)		<.0001		<.0001				.020
Black	-0.011 (0.004)	.016	0.008 (0.005)	.147			0.152 (0.055)	.006
South Asian	-0.035 (0.007)	<.0001	0.031 (0.008)	<.0001			0.160 (0.089)	.072
East Asian	-0.047 (0.011)	<.0001	0.044 (0.013)	<.0001			0.163 (0.131)	.215
Mixed	-0.015 (0.010)	.118	0.006 (0.011)	.564			0.146 (0.114)	.201
Smoking (reference non-smokers)								
Pre-existing diabetes								
Parity (reference nulliparous)		.009		<.0001		<.001		
Multiparous, previous PE/SGA	0.011 (0.007)	.092	-0.011 (0.007)	.165	-0.123 (0.081)	.131		
Multiparous, no previous PE/SGA	0.010 (0.003)	.004	-0.017 (0.004)	<.0001	-0.193 (0.043)	<.001		
Birthweight group (reference Group 5)		.019		<.0001		<.001		<.001
Group 1 (<10th percentile)	-0.035 (0.008)	<.0001	0.040 (0.009)	<.0001	-2.337 (0.101)	<.001	-0.726 (0.081)	<.001
Group 2 (10-19.9th percentile)	-0.026 (0.009)	.006	0.032 (0.010)	.002	-1.482 (0.108)	<.001	-0.657 (0.087)	<.001
Group 3 (20-29.9th percentile)	-0.022 (0.009)	.018	0.020 (0.010)	.050	-1.309 (0.108)	<.001	-0.296 (0.087)	.001
Group 4 (30-69.9th percentile)	-0.003 (0.006)	.630	0.003 (0.007)	.672	-0.732 (0.075)	<.001	-0.229 (0.060)	<.001
Hypertensive disorders (reference no)		<.0001		<.0001		.001		.008
Preeclampsia	-0.021 (0.010)	.037	0.048 (0.011)	<.0001	0.334 (0.118)	.005	-0.151 (0.120)	.210
Pregnancy-induced hypertension	-0.033 (0.009)	<.0001	0.066 (0.010)	<.0001	0.177 (0.107)	.099	0.046 (0.101)	.643
Chronic Hypertension	-0.022 (0.013)	0.089	0.064 (0.015)	<.0001	0.397 (0.157)	.012	-1.029 (0.372)	.006
Gestational diabetes	-0.025 (0.008)	.002	0.032 (0.009)	<.0001				
Time (four visits)		<.0001		<.0001		<.001		<.001
Interaction birthweight groups with time		<.0001		<.0001		<.001		.002

Estimated fetal weight and cerebroplacental ratio z-scores were assessed in three and two visits, respectively.

There was no significant contribution from smoking, pre-existing diabetes, chronic hypertension on Log_{10}Cardiac output.

There was no significant contribution from smoking, pre-existing diabetes on Log_{10} Peripheral vascular resistance.

There was no significant contribution from maternal age, race, smoking, pre-existing diabetes and gestational diabetes on estimated fetal weight z-score.

There was no significant contribution from maternal age, body surface area, smoking, parity, gestational diabetes on Cerebroplacental ratio z-score.

Table 3. Multilevel linear mixed-effects models: estimated marginal means with 95% confidence interval for maternal Log_{10} cardiac output, Log_{10} peripheral vascular resistance and estimated fetal weight and

	Visit 1	Visit 2	Visit 3	Visit 4
Log_{10} Cardiac output				
Group 1	0.716 (0.699 to 0.734)	0.735 (0.717 to 0.753)	0.725 (0.707 to 0.743)	0.704 (0.685 to 0.722)
Group 2	0.714 (0.694 to 0.733)	0.732 (0.712 to 0.752)	0.733 (0.713 to 0.753)	0.712 ‡ ++ (0.693 to 0.732)
Group 3	0.704 (0.684 to 0.723)	0.728 (0.708 to 0.748)	0.733 (0.713 to 0.753)	0.716 ‡ + (0.696 to 0.736)
Group 4	0.701 * + (0.686 to 0.716)	0.730 (0.715 to 0.745)	0.749 ** (0.734 to 0.764)	0.735 *** + $ (0.720 to 0.751)
Group 5	0.714 ‡ (0.698 to 0.730)	0.742 (0.726 to 0.758)	0.751 ** (0.735 to 0.767)	0.739 *** ++ $ (0.722 to 0.755)
Log_{10} Peripheral vascular resistance				
Group 1	3.158 (3.138 to 3.177)	3.134 (3.114 to 3.154)	3.148 (3.128 to 3.168)	3.178 (3.157 to 3.198)
Group 2	3.163 (3.141 to 3.185)	3.141 (3.119 to 3.163)	3.139 ‡ + (3.117 to 3.161)	3.170 ‡‡ ++ (3.148 to 3.192)
Group 3	3.180 (3.158 to 3.201)	3.139 (3.117 to 3.162)	3.133 (3.110 to 3.155)	3.158 (3.136 to 3.181)
Group 4	3.179 * (3.162 to 3.196)	3.138 (3.121 to 3.155)	3.118 ** (3.101 to 3.135)	3.141*** (3.123 to 3.158)
Group 5	3.170 (3.153 to 3.188)	3.129 (3.111 to 3.147)	3.117 ** (3.099 to 3.135)	3.138 *** (3.119 to 3.156)
Estimated fetal weight z-score				
Group 1		-0.701 (-0.884 to -0.519)	-0.830 +++ (-1.015 to -0.644)	-1.057 +++ (-1.246 to -0.868)
Group 2		-0.383 * (-0.588 to -0.178)	-0.138 *** ‡‡‡ +++ (-0.344 to 0.067)	-0.202 *** +++ ‡‡‡ (-0.408 to 0.002)
Group 3		-0.277 ** (-0.487 to -0.067)	-0.017 *** ‡‡‡ +++ (-0.227 to 0.192)	-0.029 *** +++ ‡‡‡ (-0.240 to 0.181)
Group 4		-0.201*** (-0.347 to -0.056)	0.492 *** +++ (0.346 to 0.638)	0.546 *** +++ (0.399 to 0.694)
Group 5		0.205 *** (0.050 to 0.361)	1.133 *** (0.975 to 1.291)	1.279 *** (1.120 to 1.438)
Cerebroplacental ratio z-score				
Group 1			-0.428 (-0.663 to -0.194)	-0.688 +++ (-0.925 to -0.451)
Group 2			-0.278 ‡ ++ (-0.523 to -0.032)	-0.618 ‡‡‡ +++ $$ (-0.863 to -0.373)
Group 3			-0.170 ** (-0.422 to 0.081)	-0.258 *** ++ (-0.510 to -0.006)
Group 4			-0.100 *** (-0.320 to 0.118)	-0.191 *** +++ (-0.410 to 0.028)
Group 5			-0.001 *** (-0.225 to 0.223)	0.038 *** (-0.185 to 0.262)

cerebroplacental ratio z-scores.

Estimated fetal weight and cerebroplacental ratio z-scores were assessed in three and two visits, respectively.

Compared to Group 1: *p<0.05, ** p<0.01, ***p<0.001; Compared to Group 5: $^{+}$p<0.05, $^{++}$p<0.01, $^{+++}$p<0.0001
Compared to Group 4: ‡p<0.05, ‡‡p<0.01, ‡‡‡ p<0.0001; Compared to Group 3: $^{\$}$p<0.05, $^{\$\$}$p<0.01, $^{\$\$\$}$ p<0.0001

Table 4 Change between visits: comparison of the Log_{10} Cardiac output and Log_{10} Peripheral vascular resistance, estimated fetal weight and cerebroplacental ratio z-scores (p-values). Estimated fetal weight and cerebroplacental ratio z-scores were assessed in three and two visits,

	Log_{10} Cardiac output					Log_{10} Peripheral vascular resistance					Estimated fetal weight z-scores					Cerebroplacental ratio z-scores		
	Visits	1	2	3	4	Visits	1	2	3	4	Visits	1	2	3	4	Visits	3	4
Group 1	1		.022	.300	.142	1		.007	.122	.162	1					1		
	2			.244	.000	2			.277	.000	2			.179	.000	2		
	3				.014	3				.003	3				.020	3		.001
	4					4					4					4		
	Visits	1	2	3	4	Visits	1	2	3	4	Visits	1	2	3	4	Visits	3	4
Group 2	1		.055	.049	.889	1		.045	.001	.959	1					1		
	2			.921	.047	2			.163	.045	2			.026	.111	2		
	3				.033	3				.001	3				.553	3		.000
	4					4					4					4		
	Visits	1	2	3	4	Visits	1	2	3	4	Visits	1	2	3	4	Visits	3	4
Group 3	1		.010	.003	.197	1		.000	.000	.018	1					1		
	2			.632	.234	2			.206	.136	2			.019	.030	2		
	3				.090	3				.005	3				.914	3		.332
	4					4					4					4		
	Visits	1	2	3	4	Visits	1	2	3	4	Visits	1	2	3	4	Visits	3	4
Group 4	1		.000	.000	.000	1		.000	.000	.000	1					1		
	2			.000	.326	2			.001	.468	2			.000	.000	2		
	3				.011	3				.000	3				.387	3		.064
	4					4					4					4		
	Visits	1	2	3	4	Visits	1	2	3	4	Visits	1	2	3	4	Visits	3	4
Group 5	1		.000	.000	.000	1		.000	.000	.000	1					1		
	2			.142	.589	2			.086	.152	2			.000	.000	2		
	3				.043	3				.001	3				.032	3		473
	4					4					4					4		

respectively.

FIGURE LEGENDS

Figure 1. Flow chart of study recruitment.

Figure 2. Linear mixed-effects model with estimated marginal means for maternal Log_{10} Cardiac output and Log_{10} Peripheral vascular resistance, estimated fetal weight z-score and Cerebroplacental ratio z-score after controlling for demographic characteristics. Group 1, birthweight less than 10th percentile (red line); group 2, 10th to 19.9th percentile (brown line); group 3, 20th to 29.9th percentile (purple line); group 4, 30th to 69.9th percentile (green line) and group 5, equal or more than the 70th centile (blue line).

Supplementary Figure 1. Linear mixed-effects model with estimated marginal means for maternal Log_{10} stroke volume, heart rate and Log_{10} mean arterial pressure in the four visits after controlling for demographic characteristics. Group 1, birthweight less than 10th percentile (red line); group 2, 10th to 19.9th percentile (brown line); group 3, 20th to 29.9th percentile (purple line); group 4, 30th to 69.9th percentile (green line) and group 5, equal or more than the 70th centile (blue line).

Supplementary Figure 2. Fetal z-scores of head circumference, abdominal circumference and femur length in the three visits after controlling for demographic characteristics. Group 1, birthweight less than 10th percentile (red line); group 2, 10th to 19.9th percentile (brown line); group 3, 20th to 29.9th percentile (purple line); group 4, 30th to 69.9th percentile (green line) and group 5, equal or more than the 70th centile (blue line).

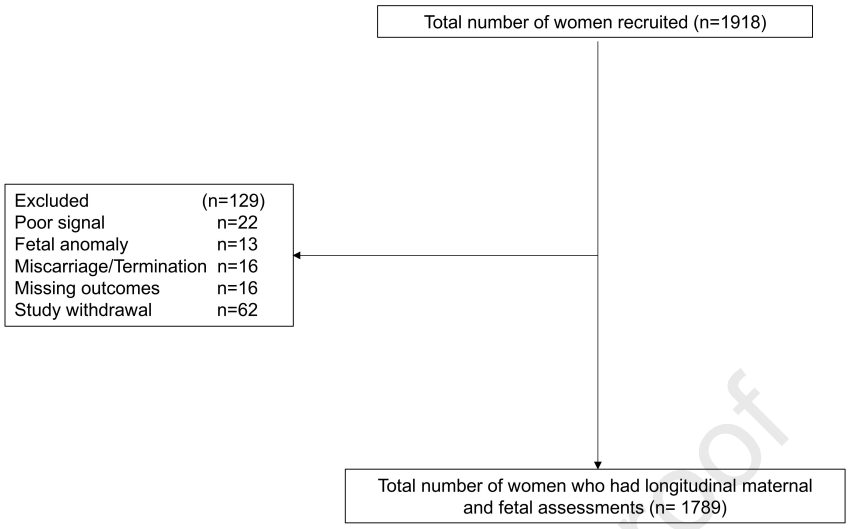

Figure 1

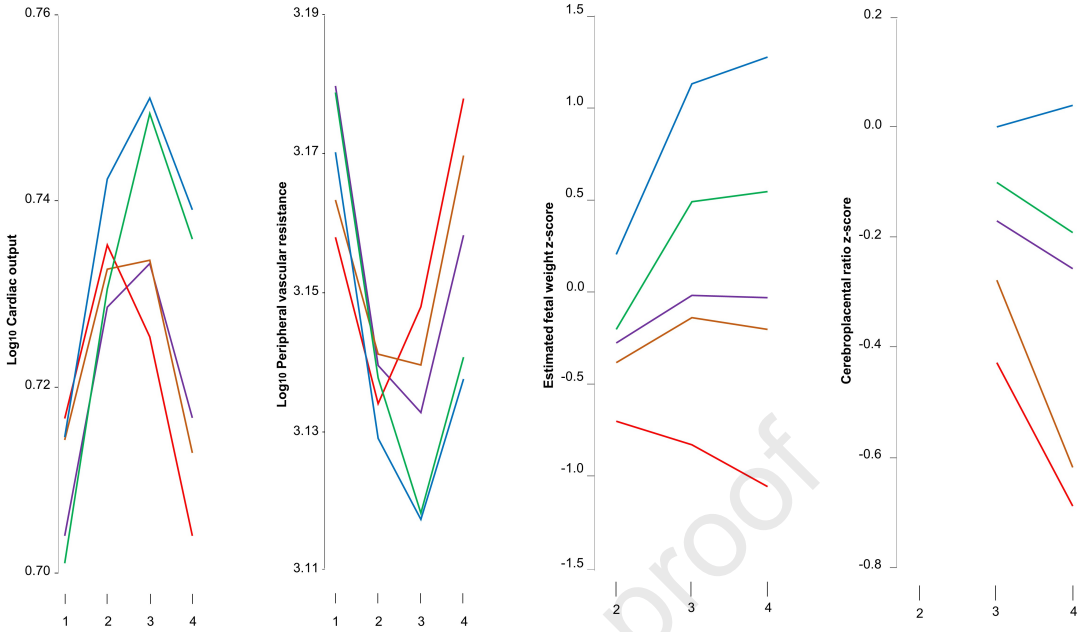

Figure 2